Pergamon

Tetrahedron: *Asymmetry* 13 (2002) 2417–2426

TETRAHEDRON: *ASYMMETRY*

A practical stereoselective synthesis of secondary and tertiary aminonaphthols: chiral ligands for enantioselective catalysts in the addition of diethylzinc to benzaldehyde

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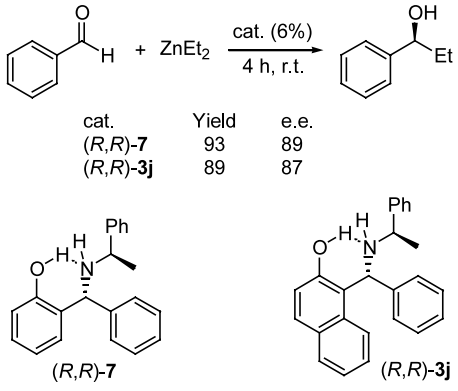
Received 3 August 2002; accepted 8 October 2002

Abstract—A practical procedure for the stereoselective synthesis of a wide group of functionalized aminoalkylnaphthols, using inexpensive starting materials, is reported. Selective *N*-alkylation was carried out by cyclization of secondary aminoalkylnaphthols with formaldehyde, followed by reduction or alkylation with organometallic reagents. The catalytic activity of this class of compounds was tested in the addition of diethylzinc to benzaldehyde, resulting in moderate to good enantioselectivities. It is noteworthy that the aminonaphthols obtained as the major diastereomer in the solvent free synthesis, have the best asymmetric induction properties in the alkylation reaction.

1. Introduction

The search for new chiral ligands, which can be efficiently applied in asymmetric catalysis, is a field of great interest in modern organic chemistry. In the last few years, the enantioselective alkylation of carbonyl compounds has been the subject of considerable development, owing to the use of dialkylzinc reagents[1–3] in the presence of a variety of chiral ligands, such as β-amino alcohols,[4–6] amino thiols[7–10] and pyridyl alcohols.[11–13] In a previous work, we have found that the enantiopure aminoalkylphenol (*R*,*R*)-**7** is a useful catalyst for the enantioselective addition of dialkylzincs to aldehydes (see Scheme 1).[14] Moreover, this class of compound can be prepared easily by the reduction[15] or alkylation[16] of 2-imidoylphenols[17,18] and by reduction of 4*H*-chromen-4-ylideneamines.[19]

Aminoalkylnaphthols, prepared for the first time by Betti at the beginning of the 20th century,[20] have recently attracted new interest due to their application in asymmetric catalysis.[14,21–25] As a result, the demand for practical and straightforward asymmetric syntheses of these compounds, starting from inexpensive reagents has increased dramatically. The condensation of 2-naphthol with ammonia and benzaldehyde produces the final 1-(α-aminobenzyl)-2-naphthol as a racemate. We have found that the condensation of 2-naphthol with benzaldehyde and (*R*)-(+)-1-phenylethylamine affords the aminonaphthol **3j** directly, practically as a single (*R*,*R*) diastereoisomer, by using a solvent free synthesis (93% yield; 99:1 d.r.).[14,22] The catalytic activity of (*R*,*R*)-**3j** in the enantioselective addition of diethylzinc to benzaldehyde is good and the corresponding (*S*)-1-phenylpropanol is obtained in 89% yield and 87% e.e.[14] Moreover, aminoalkylnaphthols can be regarded as aromatic Mannich type bases and they therefore represent useful synthetic intermediates in organic synthesis because the amino moiety can be



Scheme 1.

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PII: S0957-4166(02)00651-1

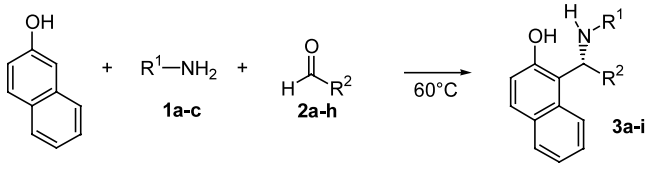
converted into a variety of other functionalities.[26,27] Herein, we report on the preparation of both secondary and tertiary, aminoalkylnaphthols, and the study of their catalytic activity towards the addition of diethylzinc to benzaldehyde.

2. Results and discussion

A series of novel secondary aminoalkylnaphthols **3a–i** were prepared by heating a mixture of 2-naphthol, amines **1a–c** and aldehydes **2a–h**, in a molar ratio 1.0:1.05:1.20, respectively, at 60°C, under solvent free conditions (see Scheme for Table 1).[14,22] The results are listed in Table 1. In the presence of (*R*)-(+)-1-phenylethylamine, aromatic aldehydes reacted with yields from moderate to good and good d.r. (Table 1, entries 1–5). When heteroaromatic aldehydes were used, the reactivity and yields decreased in relation to the heteroatom, in the order: *N*>*O*>*S*. Besides (*R*)-(+)-1-phenylethylamine, it is possible to use (*R*)-(−)-2-amino-2-phenylethanol or (*R*)-(+)-1-(1-naphthyl)ethylamine as chiral auxiliaries, (Table 1, entries 6 and 7). In both cases the yields and the stereoselectivities observed in the condensations with 2-naphthol and benzaldehyde are lower than those previously obtained with the use of (*R*)-(+)-1-phenylethylamine.[14,22]

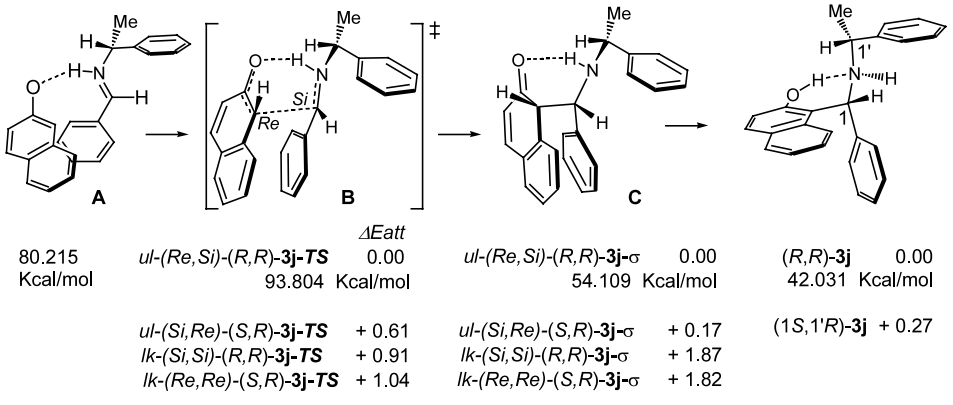
A mechanism is given in Scheme 2. It is assumed that an aldiminium type complex (**A**) is initially formed through protonation of the C=N nitrogen. In this iminium species there is an enhancement reactivity of both the electrophilic iminium carbon atom and the nucleophilic naphthol. In the first step of this Friedel–Crafts type reaction, the rate-limiting stage of the whole reaction, the arenium σ-complex *ul*-(*Re*,*Si*)-(*R*,*R*)-**3j-*σ*** (**C**) is formed through a six-membered transition state *ul*-(*Re*,*Si*)-(*R*,*R*)-**3j-*TS*** (**B**) as shown in Scheme 2. The relative stability of the transition state **3j-*TS*** calculated for all four possible combinations, at the semi-empirical PM3 level, are in agreement with the stereoselectivity observed for this Mannich type reaction. As shown in

Table 1. Synthesis of secondary aminoalkylnaphthols **3a–i**



Entry	1	R^1	2	R^2	3[a]	Time (h)	Yield[b] (%)	d.r.[c]
1	**1a**	(*R*)-PhCHMe	**2a**	2-Pyridyl	(1*S*,1′*R*)-**3a**	8	95	71/29
2	**1a**	(*R*)-PhCHMe	**2b**	2-Furyl	(1*S*,1′*R*)-**3b**	9	70	81/19
3	**1a**	(*R*)-PhCHMe	**2c**	2-Thienyl	(1*S*,1′*R*)-**3c**	18	45	84/16
4	**1a**	(*R*)-PhCHMe	**2d**	2-$MeOC_6H_5$	(1*S*,1′*R*)-**3d**	9	75	75/25
5	**1a**	(*R*)-PhCHMe	**2e**	C_6F_5	(1*S*,1′*R*)-**3e**	8	65	67/33
6	**1b**	(*R*)-$PhCHCH_2OH$	**2f**	C_6H_5	(1*S*,1′*R*)-**3f**	8	66	78/22
7	**1c**	(*R*)-(1-Naphthyl)CHMe	**2f**	C_6H_5	(*R*,*R*)-**3g**	14	80	80/20
8	**1c**	(*R*)-(1-Naphthyl)CHMe	**2g**	*i*Pr	(*R*,*R*)-**3h**	30	47	79/21
9	**1c**	(*R*)-(1-Naphthyl)CHMe	**2h**	Cyclohexyl	(*R*,*R*)-**3i**	30	48	80/20

[a] Configuration of the major diastereomer.
[b] Combined yields of the two diastereomers.
[c] The d.r. value was determined by ^1H NMR of the reaction mixture.



Scheme 2. The mechanism hypothesis for the Mannich type diastereoselective aminoalkylation of 2-naphthol, with the rationalization of the asymmetric induction on the basis of molecular modelling calculation at the semi-empirical PM3 level.

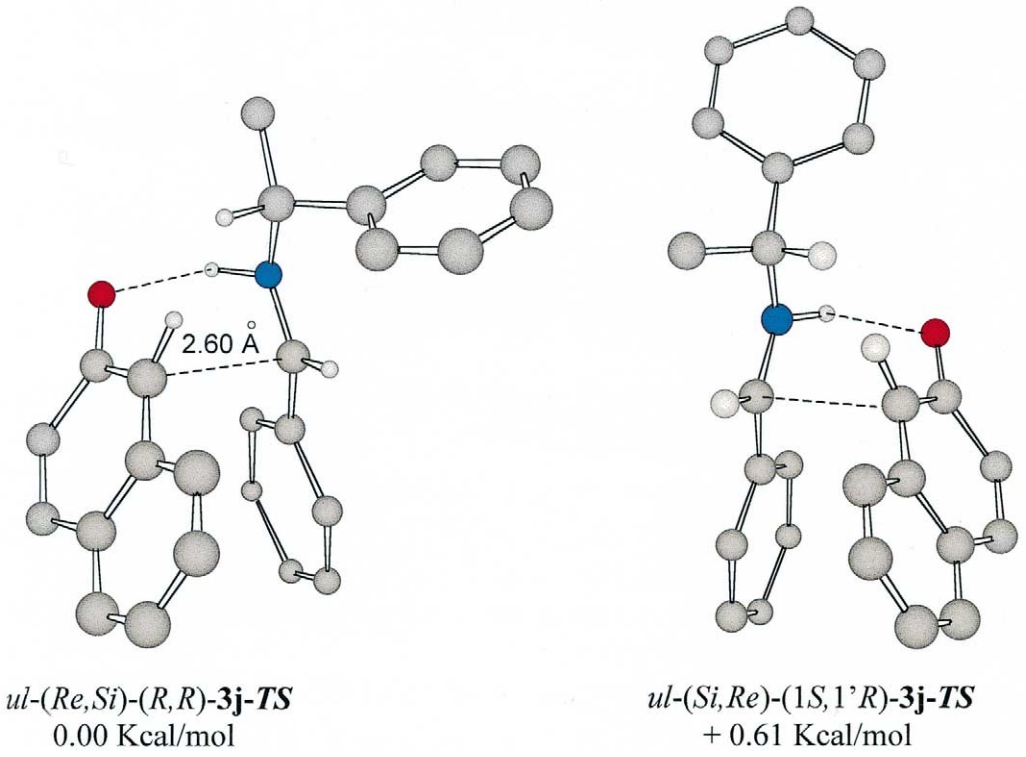


Figure 1. Unlike (*ul*) transition structures for the formation of the (*R*,*R*)- and (1*S*,1′*R*)-**3j**, optimized at the PM3 semi-empirical level (see Scheme 2).

Scheme 2 and Fig. 1 the two diastereoselective unlike approaches are favoured and, in particular the C–C forming bond lies between the α-*Re* naphthol face and the diastereotopic *Si* face of the immonium type electrophile. The moderate *ΔEatt* calculated for **3j** (0.61 kcal/mol) is in agreement with the diastereoselectivity observed experimentally for this reaction (34–68% d.e. in the Table 1). The high diastereoselectivity observed experimentally in the specific case of (*R*,*R*)-**3j** (d.e. 98%)[22] and some other aminonaphthols is due to a transformation of a second kind, induced by the preferential crystallization of the diastereomer (*R*,*R*)-**3j**.

The configuration of aminoalkylnaphthols **3a**–**i** was assigned on the basis of the general trend observed in the ^{1}H NMR chemical shifts: the signals of H-1 atom, bonded at the stereogenic C-1 carbon atom, and of H-1′ proton on the chiral auxiliary group in the major diastereomer are always shifted upfield in comparison to the corresponding signals from the minor diastereomer ($\Delta\delta$: 0.34–0.61 ppm for H-1 atom and $\Delta\delta$: 0.02–0.11 for H-1′ atom). These shifts can be rationalized by observing the preferred conformation of the respective aminoalkylnaphthols obtained by molecular modelling conformational analysis (see Fig. 2).[15,22,40] As it is possible to see, in the major diastereomer the naphthyl ring of the auxiliary amine exerts a shielding magnetic anisotropy effect on the H-1 proton while the naphthyl group shields the H-1′ proton. The validity of this diagnostic tool was confirmed by X-ray analysis on analogous aminonaphthols:[22–24] in fact, experimental structures, obtained by X-ray analysis, are very similar to those obtained by molecular modelling (see Fig. 2), thus validating the computational analysis.

Generally, it has been reported in the literature that ligands containing tertiary amino groups are better catalysts than those containing secondary ones. Thus, we became interested in the preparation of tertiary aminoalkylnaphthols. Previously these compounds were prepared by direct condensation of 2-naphthol with aldehydes and secondary amines,[28–33] aminoalkylation

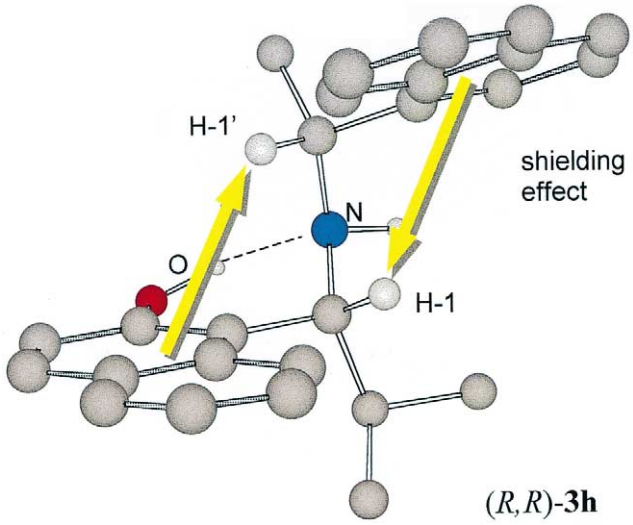
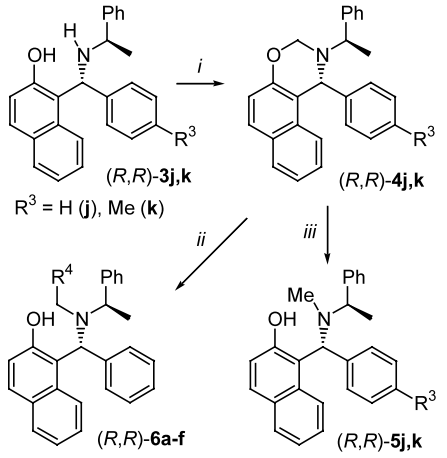


Figure 2. Conformational analysis of the aminonaphthol (*R*,*R*)-**3h**, minimized at the semi-empirical PM3 level.



Scheme 3. *Reagents and conditions*: (i) CH_2O, THF/H_2O, rt, 15 h; (ii) R_4M, toluene, 0°C; (iii) $NaBH(OAc)_3$/AcOH, THF, 0°C.

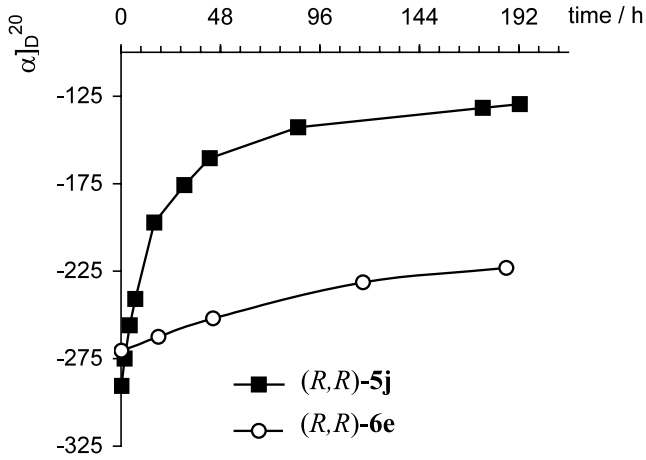


Figure 3. Epimerization of the aminonaphthols (*R*,*R*)-**5j** and (*R*,*R*)-**6e** in $CHCl_3$ solution.

of aromatic compounds with iminium salts,[34,35] by displacement of the benzotriazole moiety from *N*-[α-(dialkylamino)alkyl]benzotriazole with naphtholate anions[36] and additionally, by treatment of a protected 2-hydroxy-1-naphthaldehyde with (trimethylsilyl)-dialkylamines and various nucleophiles in the presence of lithium perchlorate.[37] All of these methods use only simple secondary amines, such as dimethylamine and diethylamine, or cyclic amines, such as morpholine and piperidine. In a previous work we developed a methodology for the preparation of tertiary aminoalkylphenols by cyclization of secondary aminoalkylphenols with formaldehyde, followed by reduction or alkylation of the intermediate benzoxazines.[38] We now report the application of this methodology to aminoalkylnaphthols. Enantiopure aminonaphthols (*R*,*R*)-**3j**,**k** can be readily cyclized with formaldehyde to naphthoxazines (*R*,*R*)-**4j**,**k**. The reduction takes place in an acidic medium (AcOH) with $NaHB(OAc)_3$ as reducting agent, affording *N*-methylaminolkylnaphthols (*R*,*R*)-**5j**,**k** (see Scheme 3 and Table 2).

The opening of the *N*-*O* cyclic acetal with organometallic reagents allows the introduction of a variety of *N*-substituents on the aminonaphthols (see Scheme 3 and Table 3). The reaction occurs in toluene at 0°C, while it fails at lower temperature (–70°C). Under these conditions the alkylation took place quickly and with high yields, except when PhLi and MeMgCl were used (Table 3, entries 4 and 5). Tertiary aminoalkylnaphthols crystallize in diastereomerically pure (*R*,*R*) form. However, when the crystals are dissolved in $CHCl_3$ or $CDCl_3$, a moderate spontaneous epimerization at the C-1 carbon atom takes place.[38,39] This phenomenon was followed by recording ^1H NMR spectra or measur-

Table 2. Reduction of 2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazines **4j**,**k** to aminonaphthols **5j**,**k**

Entry	**4**	R^3	**5**	Time (h)	Yield[a] (%)
1	(*R*,*R*)-**4j**	H	(*R*,*R*)-**5j**	4	63
2	(*R*,*R*)-**4k**	Me	(*R*,*R*)-**5k**	3	50

[a] Isolated yields.

Table 3. Alkylation of the 2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazine **4j** to aminonaphthols **6a**–**f**

Entry	R^4M	(*R*,*R*)-**6**	Time (h)	Yield[a] (%)	d.r.[b]
1	BnMgCl	(*R*,*R*)-**6a**	1	96	96/4
2	*n*-BuLi	(*R*,*R*)-**6b**	2	92	97/3
3	PhMgCl	(*R*,*R*)-**6c**	1	95	96/4
4	PhLi	(*R*,*R*)-**6c**	2	58	80/20
5	MeMgCl	(*R*,*R*)-**6d**	4	76	90/10
6	AllMgCl	(*R*,*R*)-**6e**	1	92	95/5
7	$CH_2=CHMgCl$	(*R*,*R*)-**6f**	1	98	97/3

[a] Isolated yields.
[b] The d.r. value was determined by ^1H NMR of the crude reaction mixture.

ing the specific rotation at various times, as reported in Fig. 3. When the steric hindrance from the *N*-substituent increases, the epimerization becomes more important: in fact after 15 days a solution of *N*-methylaminonaphthol (*R*,*R*)-**5j** results in a mixture of (*R*,*R*)- and (1*S*,1′*R*)-**5j** with d.r. of 82:18, while after 8 days only *N*-3-butenylaminonaphthol (*R*,*R*)-**6e** affords a diastereomeric mixture of 75:25, with (*R*,*R*)-**6e** as the major diastereomer.

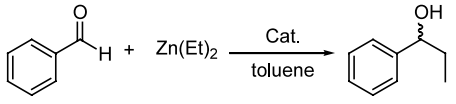
The catalytic activity of these aminoalkylnaphthols was tested in the enantioselective addition of diethylzinc to benzaldehyde. The results obtained are reported in Table 4. The stereoselectivity of the addition increases with the use of larger amounts of the aminoalkylnaphthol as catalyst (Table 4, entries 13–15). The use of 10 mol% of ligand is the better compromise solution for (*R*,*R*)-**5j**; a greater quantity (15 mol%) of (*R*,*R*)-**5j** only leads to a moderate increase in the stereoselectivity (86% e.e.), significantly lower than that reported by Wang and co-workers.[24]

With the secondary aminoalkylnaphthols derived from heteroaromatic aldehydes, the stereoselectivity is lower (Table 4, entries 1–4) than that observed for (*R*,*R*)-**3j**.[14] Therefore, the introduction of a third coordination site in the ligand does not afford better catalytic activity. Aminolkylnaphthols (1*S*,1′*R*)-**3d** and (1*S*,1′*R*)-**3e**, containing $R^2 = o\text{-}MeC_6H_4$ and $R^2 = C_6F_5$, gave higher enantioselectivities, affording the (*S*)-1-phenylpropanol with 89 and 87% e.e., respectively. Both diastereomers of compound **3d** were tested in the addition reaction (Table 4, entries 5 and 6), affording alcohols of opposite configuration and with very different enantioselectivities. It is notable that the 1*S*,1′*R* diastereomer, the one obtained as major product in the solvent free synthesis, gives the best asymmetric induction in the alkylation reaction. The change of the (*R*)-(+)-1-phenylethylamine chiral auxiliary with (*R*)-(−)-2-amino-2-phenylethanol produces ligands (1*S*,1′*R*)-**3f** and (*R*,*R*)-**3f** which gave poor asymmetric induction. On the other hand the aminolkylnaphthol (*R*,*R*)-**3g** containing the (1-naphthyl)ethyl group affords the (*S*)-1-phenylpropanol with a good 81% e.e. Aromatic R^2 substituents on aminoalkylnaphthols are better substituents than aliphatic ones and determinate higher enantioselectivities (Table 4, entries 10–12). Tertiary aminoalkylnaphthols produce enantioselectivities from moderate to good (58–85% e.e.). The best results were obtained using compounds (*R*,*R*)-**5j**,**k** and (*R*,*R*)-**6f**, which have *N*-Me and *N*-allyl groups. Lengthening of the aliphatic chain on the amino moiety, such as in (*R*,*R*)-**6b** and (*R*,*R*)-**6e**, led to a slight decrease in the stereoselectivity.

3. Conclusion

In summary a practical procedure for the stereoselective synthesis of a wide group of functionalized aminoalkyl-

Table 4. Diethylzinc addition to benzaldehyde in the presence of aminoalkylnaphthols **3**, **5**, **6**



Entry	Cat.	Mol. (%)	Time (h)	Yield[a] (%)	% e.e.[b]	Config.[c]
1	(1*S*,1′*R*)-**3a**	10	24	86	20	*R*
2	(*R*,*R*)-**3a**	10	4	86	16	*S*
3	(1*S*,1′*R*)-**3b**	10	7	53	60	*S*
4	(1*S*,1′*R*)-**3c**	10	17	87	58	*S*
5	(1*S*,1′*R*)-**3d**	10	4	81	89	*S*
6	(*R*,*R*)-**3d**	10	4	79	16	*R*
7	(1*S*,1′*R*)-**3e**	10	24	85	87	*S*
8	(1*S*,1′*R*)-**3f**	10	4	26	12	*S*
9	(*R*,*R*)-**3f**	10	24	68	15	*S*
10	(*R*,*R*)-**3g**	10	4	84	81	*S*
11	(*R*,*R*)-**3h**	10	7	73	17	*S*
12	(*R*,*R*)-**3i**	10	7	77	40	*S*
13	(*R*,*R*)-**5j**	6	4	97	74	*S*
14	(*R*,*R*)-**5j**	10	4	87	84	*S*
15	(*R*,*R*)-**5j**	15	2	90	86	*S*
16	(*R*,*R*)-**5k**	10	5	97	85	*S*
17	(*R*,*R*)-**6a**	10	5	95	72	*S*
18	(*R*,*R*)-**6b**	10	5	84	77	*S*
19	(*R*,*R*)-**6c**	10	5	88	58	*S*
20	(*R*,*R*)-**6e**	10	5	93	78	*S*
21	(*R*,*R*)-**6f**	10	5	86	85	*S*

[a] Isolated yields.

[b] Determined by integration of peaks in GLC using a chiral stationary phase.[41]

[c] Absolute configuration of the obtained major enantiomer determined by the sign of the specific rotation and the relative retention times in capilliary chiral phase GLC analysis.[41]

naphthols from inexpensive starting materials is reported. Selective *N*-alkylation was carried out by cyclization of secondary aminoalkylnaphthols with formaldehyde, followed by reduction or alkylation with organometallic reagents. The catalytic activity of this class of compounds was tested in the addition of diethylzinc to benzaldehyde, resulting in moderate to good enantioselectivities. It is worth noting that the aminonaphthols, obtained as major diastereomers in the solvent free synthesis gave the best asymmetric induction in the alkylation.

4. Experimental

4.1. General methods

^{1}H and ^{13}C NMR spectra were recorded at 200 or 300 MHz and 50 or 75 MHz, respectively. Chemical shifts are given in ppm downfield from Me_4Si in $CDCl_3$ solution. Coupling constants are given in Hz. IR spectra were recorded using a FTIR apparatus. Optical rotations were measured in a 1 dm cell at 20°C. All melting points were uncorrected. All reagents were commerially available, were purchased at the highest quality and were purified by distillation when necessary. THF and toluene were distilled and stored on sodium wire before use. The following organometallic reagents were used: BuLi (2.5 M, solution in hexane), PhLi (1.8 M, solution in cyclohexane/diethylether), MeMgCl (3.0 M, solution in THF), AllMgCl (2.0 M, solution in THF), VinylMgCl (1.6 M, solution in THF), PhMgCl (2.0 M, solution in THF), BnMgCl (2.0 M, solution in THF). Commercial (*R*)-(+)-1-phenylethylamine (96% e.e.) was used. Where only the major diastereomer was obtained pure, the ^{1}H NMR signals for the minor diastereomer were deduced from the spectra of the crude reaction mixture or from enriched chromatographic fractions.

4.2. General procedure for the preparation of aminoalkylnaphthols 3a–k

A mixture of 2-naphthol (0.72 g, 5.0 mmol), amine **1a**–**c** (5.25 mmol) and aldehyde **2a**–**h** (6.0 mmol) was stirred at 60°C under a nitrogen atmosphere for the time required (see Table 1). Aminoalkylnaphthols **3a**–**i** were purified by flash cromatography directly from the reaction mixture, without any work-up. Spectral data of (*R*,*R*)-**3j** and (*R*,*R*)-**3k** were according to those reported in Ref. 22. The characterization of the newly prepared aminolkylnaphthols **3a**–**i** follows.

4.2.1. 1-[(*S*)-{[(1′*R*)-1′-Phenylethyl]amino}(pyridin-2-yl)methyl]-2-naphthol, (1*S*,1′*R*)-3a. White crystals; mp 135–138°C (EtOH); $[\alpha]_D^{20}=+10.9$ (*c* 1.9, $CHCl_3$); IR (Nujol): ν_{max} 3291, 1621, 1590, 1272, 1237, 748 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.55 (d, 3H, $J=7.0$ Hz), 3.91 (q, 1H, $J=7.0$ Hz), 4.25 (br s, 1H), 5.54 (s, 1H), 6.63 (d, 1H, $J=7.9$ Hz), 7.00–8.65 (m, 14H), 13.45 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.7, 55.5, 58.6, 113.4, 120.2, 121.1, 121.8, 122.3, 122.5, 126.7, 126.8, 127.5, 128.5, 128.7, 128.8, 130.0, 133.7, 136.8, 143.2, 148.6, 157.6, 159.2. Anal. calcd for $C_{24}H_{22}N_2O$ (354.4): C, 81.33; H, 6.26; N, 7.90. Found: C, 81.42; H, 6.39; N, 7.75%.

4.2.2. 1-[(*R*)-{[(1′*R*)-1′-Phenylethyl]amino}(pyridin-2-yl)methyl]-2-naphthol, (1*R*,1′*R*)-3a. Oil; $[\alpha]_D^{20}=+4.3$ (*c* 1.9, $CHCl_3$); IR (liquid film): ν_{max} 3298, 1620, 1592, 1270, 1236, 749 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.64 (d, 3H, $J=6.6$ Hz), 4.00 (q, 1H, $J=6.6$ Hz), 4.25 (br s, 1H), 6.04 (s, 1H), 6.83 (d, 1H, $J=8.1$ Hz), 7.10–8.70 (m, 14H), 13.45 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.6, 55.4, 59.6, 113.6, 120.3, 120.9, 122.1, 122.5, 122.6, 126.7, 126.8, 127.3, 128.4, 128.5, 128.9, 129.9, 133.3, 137.2, 143.5, 148.8, 157.1, 159.5. Anal. calcd for $C_{24}H_{22}N_2O$ (354.4): C, 81.33; H, 6.26; N, 7.90. Found: C, 81.21, H 6.40, N 7.95%.

4.2.3. 1-[(*S*)-2-Furyl{[(1′*R*)-1′-phenylethyl]amino}-methyl]-2-naphthol, (1*S*,1′*R*)-3b. Yellow crystals; mp 87–89°C (EtOH); $[\alpha]_D^{20}=-121.7$ (*c* 2.1, $CHCl_3$); IR (Nujol): ν_{max} 3312, 1622, 1601, 1265, 1235, 738 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.52 (d, 3H, $J=6.9$ Hz), 2.76 (br s, 1H), 3.87 (br q, 1H, $J=6.9$ Hz), 5.59 (s, 1H), 5.77 (d, 1H, $J=3.3$ Hz), 6.17 (dd, 1H, $J=3.3$, 1.9 Hz), 7.15–7.40 (m, 10H), 7.70–7.80 (m, 2H), 13.00 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.7, 53.6, 56.1, 108.4, 111.1, 111.7, 120.5, 121.4, 123.0, 127.0, 127.1, 128.3, 129.0, 129.2, 129.4, 130.6, 133.2, 142.8, 143.2, 154.0, 157.9. Anal. calcd for $C_{23}H_{21}NO_2$ (343.4): C, 80.44; H, 6.16; N, 4.08. Found: C, 80.57; H, 6.09; N, 4.00%.

4.2.4. 1-[(*R*)-2-Furyl{[(1′*R*)-1′-phenylethyl]amino}-methyl]-2-naphthol, (*R*,*R*)-3b. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.58 (d, 3H, $J=6.6$ Hz), 2.76 (br s, 1H), 3.95 (q, 1H, $J=6.6$ Hz), 5.95 (d, 1H, $J=3.3$ Hz), 5.99 (s, 1H), 6.22 (dd, 1H, $J=3.3$, 2.0 Hz), 7.15–7.40 (m, 10H), 7.70–7.80 (m, 2H), 13.00 (br s, 1H).

4.2.5. 1-[(*S*)-2-Thienyl{[(1′*R*)-1′-phenylethyl]amino}-methyl]-2-naphthol, (1*S*,1′*R*)-3c. White crystals; mp 133–136°C (CH_2Cl_2–hexane); $[\alpha]_D^{20}=-154.6$ (*c* 1.3, $CHCl_3$); IR (Nujol): ν_{max} 3272, 1624, 1602, 1268, 1240, 1092, 747, 703 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.52 (d, 3H, $J=6.9$ Hz), 2.47 (br s, 1H), 3.89 (br s, 1H), 5.73 (s, 1H), 6.80–7.80 (m, 14H), 13.30 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.6, 55.2, 56.7, 114.1, 120.6, 121.3, 123.0, 125.6, 125.9, 127.0, 127.1, 127.4, 128.4, 129.1, 129.3, 129.5, 130.5, 132.8, 143.3, 145.4, 157.2. Anal. calcd for $C_{23}H_{21}NOS$ (359.5): C, 76.84; H, 5.89; N, 3.90; S 8.92. Found: C, 76.70; H, 5.97; N, 3.98, S 8.71%.

4.2.6. 1-[(*R*)-2-Thienyl{[(1′*R*)-1′-phenylethyl]amino}-methyl]-2-naphthol, (1*R*,1′*R*)-3c. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.59 (d, 3H, $J=6.6$ Hz), 2.47 (br s, 1H), 4.00 (q, 1H, $J=6.6$ Hz), 6.13 (s, 1H), 6.80–7.80 (m, 14H), 13.30 (br s, 1H).

4.2.7. 1-[(*S*)-(2-Methoxyphenyl){[(1′*R*)-1′-phenylethyl]-amino}methyl]-2-naphthol, (1*S*,1′*R*)-3d. White crystals; mp 146–149°C (EtOH); $[\alpha]_D^{20}=-267.5$ (*c* 1.7, $CHCl_3$); IR (Nujol): ν_{max} 3294, 1621, 1600, 1241, 1097, 1028, 742

cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.49 (d, 3H, $J=6.8$ Hz), 2.52 (br s, 1H), 3.74 (s, 3H), 3.89 (br s, 1H), 5.86 (s, 1H), 6.60–7.80 (m, 15H), 13.80 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.9, 54.8, 55.5, 57.3, 110.8, 113.5, 120.4, 121.5, 121.8, 122.9, 126.8, 127.8, 128.1, 128.6, 128.8, 129.1, 129.5, 129.7, 129.9, 130.1, 133.2, 143.3, 157.0, 158.5. Anal. calcd for $C_{26}H_{25}NO_2$ (383.5): C, 81.43; H, 6.57; N, 3.65. Found: C, 81.60; H, 6.63; N, 3.60%.

4.2.8. 1-[(*R*)-(2-Methoxyphenyl){[(1′*R*)-1′-phenylethyl]-amino}methyl]-2-naphthol, (*R*,*R*)-3d. White crystals; mp 151–155°C (EtOH); $[\alpha]_D^{20}=+213.2$ (c 2.2, $CHCl_3$); IR (Nujol): ν_{max} 3293, 1620, 1600, 1243, 1095, 1028, 740 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.64 (d, 3H, $J=6.6$ Hz), 2.30 (br s, 1H), 4.00 (q, 1H, $J=6.6$ Hz), 4.04 (s, 3H), 6.42 (s, 1H), 6.70–7.80 (m, 15H), 13.50 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.1, 54.1, 55.5, 55.8, 110.4, 113.1, 120.1, 121.2, 121.3, 122.3, 126.4, 126.5, 126.7, 127.2, 128.3, 128.5, 128.6, 128.7, 129.3, 129.5, 132.8, 143.8, 156.4, 157.8. Anal. calcd for $C_{26}H_{25}NO_2$ (383.5): C, 81.43; H, 6.57; N, 3.65. Found: C, 81.50; H, 6.49; N, 3.57%.

4.2.9. 1-[(*S*)-(2,3,4,5,6-Pentafluorophenyl){[(1′*R*)-1′-phenylethyl]amino}methyl]-2-naphthol, (1*S*,1′*R*)-3e. White crystals; mp 159–163°C (CH_2Cl_2–hexane); $[\alpha]_D^{20}=-251.0$ (c 1.1, $CHCl_3$); IR (Nujol): ν_{max} 3292, 1653, 1624, 1602, 1274, 1237, 820, 745, 701 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.57 (d, 3H, $J=6.6$ Hz), 2.15 (br s, 1H), 3.99 (m, 1H), 5.91 (s, 1H), 7.10–7.80 (m, 11H), 13.05 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.8, 50.6, 57.0, 108.6, 115.2 (m), 119.7, 120.2, 122.5, 126.5, 127.0, 128.2, 128.6, 129.0, 129.1, 130.5, 132.2, 137.6 (dm, $J=247.6$), 141.0 (dm, $J=248.8$), 141.9, 145.03 (dm, $J=252.0$), 158.1. Anal. calcd for $C_{25}H_{18}F_5NO$ (443.4): C, 67.72; H, 4.09; N, 3.16. Found: C, 67.90; H, 4.15; N, 3.12%.

4.2.10. 1-[(*R*)-(2,3,4,5,6-Pentafluorophenyl){[(1′*R*)-1′-phenylethyl]amino}methyl]-2-naphthol, (*R*,*R*)-3e. White crystals; mp 142–144°C (CH_2Cl_2–hexane); $[\alpha]_D^{20}=+226.4$ (c 1.0, $CHCl_3$); IR (Nujol): ν_{max} 3301, 1652, 1624, 1522, 1275, 1236, 820, 747, 701 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.63 (d, 3H, $J=6.6$ Hz), 2.15 (br s, 1H), 4.04 (q, 1H, $J=6.6$), 6.29 (s, 1H), 7.05–7.80 (m, 11H), 12.60 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.6, 51.0, 56.3, 109.6, 115.5 (tm, $J=16.5$), 120.0, 120.7, 122.7, 126.6, 127.2, 128.1, 128.7, 129.1, 129.3, 130.7, 132.2, 140.0 (dm, $J=253.1$), 141.2 (dm, $J=253.7$), 142.4, 142.9 (dm, $J=249.2$), 157.8. Anal. calcd for $C_{25}H_{18}F_5NO$ (443.4): C, 67.72; H, 4.09; N, 3.16. Found: C, 67.88; H, 4.01; N, 3.09%.

4.2.11. 1-[(*S*)-Phenyl{[(1′*R*)-2-hydroxy-1′-phenylethyl]-amino}methyl]-2-naphthol, (1*S*,1′*R*)-3f. Oil; $[\alpha]_D^{20}=+139.4$ (c 2.9, $CHCl_3$); IR (liquid film): ν_{max} 3309, 1622, 1601, 1269, 1236, 736, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.78–4.00 (m, 3H), 4.50–6.30 (br s, 3H), 5.55 (s, 1H), 7.15–7.75 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 60.5, 63.0, 66.8, 113.6, 120.5, 121.6, 123.0, 127.0, 128.1, 128.2, 128.6, 128.9, 129.0, 129.1, 129.3, 129.6, 130.4, 133.1, 139.4, 141.6, 157.2. Anal. calcd for $C_{25}H_{23}NO_2$ (369.5): C, 81.27; H, 6.27; N, 3.79. Found: C, 81.34; H, 6.15; N, 3.61%.

4.2.12. 1-[(*R*)-Phenyl{[(1′*R*)-2-hydroxy-1′-phenylethyl]-amino}methyl]-2-naphthol, (*R*,*R*)-3f. Oil; $[\alpha]_D^{20}=-179.3$ (c 1.3, $CHCl_3$); IR (liquid film): ν_{max} 3307, 1620, 1603, 1268, 1237, 735, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.78–4.00 (m, 2H), 4.05–4.10 (m, 1H), 4.50–6.30 (br s, 3H), 5.91 (s, 1H), 7.15–7.75 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 61.0, 62.0, 65.0, 114.9, 120.7, 121.6, 122.9, 127.0, 127.7, 128.4, 128.5, 129.1, 129.2, 129.3, 129.5, 129.7, 130.2, 132.8, 139.4, 141.5, 157.0. Anal. calcd for $C_{25}H_{23}NO_2$ (369.5): C, 81.27, H 6.27, N 3.79. Found: C, 81.33; H, 6.21; N, 3.89%.

4.2.13. 1-[(*R*)-Phenyl{[(1′*R*)-1′-(1-naphthyl)ethyl]amino}-methyl]-2-naphthol, (*R*,*R*)-3g. White crystals; mp 159–162°C (CH_2Cl_2–hexane); $[\alpha]_D^{20}=-288.1$ (c 1.0, $CHCl_3$); IR (Nujol): ν_{max} 3320, 1621, 1589, 1270, 1237, 779, 744 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.65 (d, 3H, $J=6.6$ Hz), 2.61 (br s, 1H), 4.90 (m, 1H), 5.51 (s, 1H), 7.00–7.95 (m, 18H), 13.95 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.1, 51.3, 61.2, 113.5, 120.1, 121.2, 122.3, 122.5, 125.3, 125.6, 125.7, 125.8, 126.2, 126.3, 127.7, 128.0, 128.2, 128.3, 128.6, 128.7, 128.9, 129.1, 129.8, 132.1, 132.6, 141.6, 157.2. Anal. calcd for $C_{29}H_{25}NO$ (403.5): C, 86.32; H, 6.24; N, 3.47. Found: C, 86.47; H, 6.29; N, 3.33%.

4.2.14. 1-[(*S*)-Phenyl{[(1′*R*)-1′-(1-naphthyl)ethyl]amino}-methyl]-2-naphthol, (1*S*,1′*R*)-3g. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.70 (d, 3H, $J=6.6$ Hz), 2.00 (br s, 1H), 4.89 (m, 1H), 5.99 (s, 1H), 7.00–8.00 (m, 18H), 13.30 (br s, 1H).

4.2.15. 1-[(1*R*)-2-Methyl-1-{[(1′*R*)-1′-(1-naphthyl)ethyl]-amino}propyl]-2-naphthol, (*R*,*R*)-3h. White crystals; mp 147–150°C (hexane); $[\alpha]_D^{20}=-193.1$ (c 0.9, $CHCl_3$); IR (Nujol): ν_{max} 3326, 2962, 1621, 1599, 1270, 1236, 778, 745 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.76 (d, 3H, $J=7.0$ Hz), 0.99 (d, 3H, $J=6.6$ Hz), 1.62 (d, 3H, $J=6.6$ Hz), 2.07–2.32 (m, 1H), 2.52 (br s, 1H), 4.21 (d, 1H, $J=5.9$ Hz), 4.68 (br s, 1H), 7.00–7.95 (m, 13H), 13.40 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.3, 20.4, 23.4, 32.9, 50.2, 61.7, 115.2, 119.9, 121.8, 122.2, 122.7, 125.7, 125.9, 126.0, 126.3, 128.1, 128.7, 128.8, 128.9, 129.0, 129.3, 131.6, 133.5, 134.0, 140.3, 156.9. Anal. calcd for $C_{26}H_{27}NO$ (369.5): C, 84.51; H, 7.37; N, 3.79. Found: C, 84.37; H, 7.45; N, 3.86%.

4.2.16. 1-[(1*S*)-2-Methyl-1-{[(1′*R*)-1′-(1-naphthyl)ethyl]-amino}propyl]-2-naphthol, (1*S*,1′*R*)-3h. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (d, 3H, $J=7.0$ Hz), 1.11 (d, 3H, $J=6.6$ Hz), 1.64 (d, 3H, $J=6.6$ Hz), 2.15–2.50 (m, 2H), 4.75 (q, 1H, $J=6.6$ Hz), 4.81 (d, 1H, $J=6.2$ Hz), 7.00–8.00 (m, 13H), 12.80 (br s, 1H).

4.2.17. 1-[(1*R*)-Cyclohexyl{[(1′*R*)-1′-(1-naphthyl)ethyl]-amino}methyl]-2-naphthol, (*R*,*R*)-3i. White crystals; mp 155–158°C (CH_2Cl_2); $[\alpha]_D^{20}=-227.5$ (c 1.03, $CHCl_3$); IR (Nujol): ν_{max} 3337, 2923, 1619, 1597, 1578, 1269, 1235, 780, 749 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90–1.35 (m, 6H), 1.50–1.97 (m, 5H), 1.60

(d, 3H, $J=7.0$ Hz), 2.59 (br s, 1H), 4.22 (d, 1H, $J=5.9$ Hz), 4.67 (br s, 1H), 7.00–7.90 (m, 13H), 13.40 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.4, 26.1, 26.2, 26.3, 28.9, 30.5, 42.6, 50.0, 60.9, 115.0, 119.7, 121.7, 122.0, 122.6, 125.5, 125.6, 125.7, 126.0, 127.9, 128.5, 128.6, 128.7, 128.8, 129.1, 131.3, 133.4, 133.8, 140.3, 156.8. Anal. calcd for $C_{29}H_{31}NO$ (409.6): C, 85.04; H, 7.63; N, 3.42. Found: C, 84.91; H, 7.84; N, 3.49%.

4.2.18. 1-[(1*S*)-Cyclohexyl{[(1′*R*)-1′-(1-naphthyl)ethyl]-amino}methyl]-2-naphthol, (1*S*,1′*R*)-3i. Oil; $[\alpha]_D^{20}=+33.2$ (c 1.0, $CHCl_3$); IR (liquid film): ν_{max} 3331, 2922, 1621, 1599, 1519, 1269, 1234, 778, 741 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.00–1.50 (m, 6H), 1.55–2.10 (m, 5H), 1.63 (d, 3H, $J=6.6$ Hz), 2.25 (br s, 1H), 4.69 (q, 1H, $J=6.6$ Hz), 4.83 (d, 1H, $J=6.2$ Hz), 7.00–8.00 (m, 13H), 12.70 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.9, 26.2, 26.3, 26.4, 29.4, 30.7, 42.5, 49.6, 60.0, 115.0, 120.1, 121.5, 122.1, 122.2, 122.9, 125.3, 125.6, 126.1, 126.2, 127.8, 128.6, 128.9, 129.0, 129.1, 130.6, 133.5, 133.9, 140.2, 156.8. Anal. calcd for $C_{29}H_{31}NO$ (409.6): C, 85.04; H, 7.63; N, 3.42. Found: C, 85.19; H, 7.78; N, 3.30%.

4.3. General procedure for the preparation of the naphthoxazines (*R*,*R*)-4j,k

Aminonaphthols (*R*,*R*)-**3j**,**k** (2 mmol) were dissolved in THF (3 mL) and 35% aqueous formaldehyde (0.17 mL, 2.2 mmol) was added. The solution was stirred for 15 hours at room temperature. Solvent was removed and the residue was dried under reduced pressure. The crude oil was purified by filtration through a SiO_2 pad eluting with cyclohexane/AcOEt (97/3). Spectral data of (*R*,*R*)-**4j** were according to that reported in Ref. 22. The characterization of the newly prepared naphthoxazine (*R*,*R*)-**4k** follows.

4.3.1. (1*R*)-1-(4-Methylphenyl)-2-[(1′*R*)-1′-phenylethyl]-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazine, (*R*,*R*)-4k. White crystals; mp 125–127°C (EtOH); $[\alpha]_D^{20}=-177.7$ (c 1.0, $CHCl_3$); IR (Nujol): ν_{max} 3022, 2974, 1509, 1233, 950, 907 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.59 (d, 3H, $J=6.6$ Hz), 2.32 (s, 3H), 4.02 (q, 1H, $J=6.6$ Hz), 5.01 (d, 1H, $J=10.3$ Hz), 5.19 (dd, 1H, $J=10.3$, 1.8 Hz), 5.21 (s, 1H), 6.90–7.50 (m, 13H), 7.80–7.90 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.1, 21.7, 56.9, 59.1, 74.4, 112.4, 118.5, 122.6, 123.1, 126.5, 127.5, 127.8, 127.9, 128.5, 128.6, 128.7, 128.8, 129.0, 132.9, 136.8, 140.3, 145.5, 152.8. Anal. calcd for $C_{27}H_{25}NO$ (379.5): C, 85.45; H, 6.64; N, 3.69. Found: C, 85.32; H, 6.79; N, 3.77%.

4.4. General procedure for the reduction of the naphthoxazines (*R*,*R*)-4j,k

To a solution of naphthoxazine (*R*,*R*)-**4j**,**k** (2.0 mmol) in THF (3.5 mL), $NaBH_4$ (0.151 g, 4.0 mmol) was added. Then the reaction mixture, cooled to 0°C, was vigorously stirred and a solution of AcOH (2 mL) in THF (3 mL) was slowly added. At the end of the addition, the temperature of the mixture was raised to room temperature. The course of the reaction was monitored by TLC, until complete consumption of the starting naphthoxazine. Then saturated Na_2CO_3 was added and when the development of CO_2 was ceased the organic layer was extracted with CH_2Cl_2, dried with anhydrous Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The chromatographic purification over SiO_2 (cyclohexane–AcOEt = 90:10) of the crude oil afforded the *N*-methylaminonaphthols (*R*,*R*)-**5j**,**k**.

4.4.1. 1-[(1*R*)-Phenyl{methyl[(1′*R*)-1′-phenylethyl]-amino}methyl]-2-naphthol, (*R*,*R*)-5j. White crystals; mp 157–160°C (CH_2Cl_2–hexane); $[\alpha]_D^{20}=-270.5$ (c 1.0, $CHCl_3$); IR (Nujol): ν_{max} 1622, 1601, 1267, 1237, 736, 701 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.55 (d, 3H, $J=6.6$ Hz), 2.14 (s, 3H), 4.25 (br q, 1H, $J=6.6$ Hz), 5.37 (s, 1H), 7.10–8.00 (m, 16H), 14.00 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.0, 33.2, 57.4, 68.6, 116.4, 120.2, 121.2, 122.6, 126.7, 127.9, 128.2, 128.4, 128.5, 128.8, 129.0, 129.1, 129.2, 129.3, 129.8, 132.3, 140.3, 156.1. Anal. calcd for $C_{26}H_{25}NO$ (367.5): C, 84.98; H, 6.86; N, 3.81. Found: C, 84.79; H, 7.12; N, 3.69%.

4.4.2. 1-[(1*R*)-(4-Methylphenyl){methyl[(1′*R*)-1′-phenylethyl]amino}methyl]-2-naphthol, (*R*,*R*)-5k. White crystals; mp 155–160°C (hexane); $[\alpha]_D^{20}=-238.5$ (c 1.08, $CHCl_3$); IR (Nujol): ν_{max} 1621, 1600, 1581, 1519, 1267, 1237, 819, 742 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.54 (d, 3H, $J=7.0$ Hz), 2.14 (s, 3H), 2.26 (s, 3H), 4.24 (q, 1H, $J=7.0$ Hz), 5.34 (s, 1H), 7.00–8.00 (m, 15H), 14.10 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.0, 21.2, 33.1, 57.2, 68.3, 116.6, 120.1, 121.2, 122.6, 123.0, 126.6, 127.8, 128.5, 128.6, 129.0, 129.2, 129.3, 129.6, 131.4, 132.3, 137.2, 137.8, 156.0. Anal. calcd for $C_{27}H_{27}NO$ (381.5): C, 85.00; H, 7.13; N, 3.67. Found: C, 85.12; H, 7.03; N, 3.59%.

4.5. General procedure for the alkylation of the naphthoxazine (*R*,*R*)-4j with organometallic reagents

The naphthoxazine (*R*,*R*)-**4j** (2.0 mmol) was dissolved in anhydrous toluene (3 mL) under a nitrogen atmosphere and then cooled to 0°C with an ice-water bath. Then the organometallic reagent (1.5 mmol) was added and the solution was stirred at 0°C for 1 hour. The reaction mixture was quenched with saturated aqueous ammonium chloride (10 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The organic layer was dried with anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The tertiary aminonaphthols (*R*,*R*)-**6a**–**c** and (*R*,*R*)-**6e** were purified by crystallization from the crude oil.

4.5.1. 1-[(1*R*)-Phenyl{phenethyl[(1′*R*)-1′-phenylethyl]-amino}methyl]-2-naphthol, (*R*,*R*)-6a. White crystals; mp 122–125°C (hexane); $[\alpha]_D^{20}=-295.0$ (c 1.0, $CHCl_3$); IR (Nujol): ν_{max} 1621, 1600, 1583, 1453, 1267, 1236, 745, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.62 (d, 3H, $J=7.0$ Hz), 2.19–2.30 (m, 1H), 2.35–2.65 (m, 2H), 3.00–3.25 (m, 1H), 4.33 (q, 1H, $J=7.0$ Hz), 5.52 (s, 1H), 6.70 (d, 2H, $J=7.32$ Hz), 7.00–7.90 (m, 19H), 13.90 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ

19.1, 38.1, 48.1, 58.8, 67.7, 116.4, 119.9, 121.0, 122.5, 126.1, 126.5, 127.9, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 128.9, 129.0, 129.7, 130.2, 130.4, 131.8, 139.6, 156.4. Anal. calcd for $C_{33}H_{31}NO$ (457.6): C, 86.61; H, 6.83; N, 3.06. Found: C, 86.73; H, 6.94; N, 2.94%.

4.5.2. 1-[(1*R*)-Phenyl{pentyl[(1′*R*)-1′-phenylethyl]amino}-methyl]-2-naphthol, (*R*,*R*)-6b. White crystals; mp 103–106°C (hexane); $[\alpha]_D^{20}=-256.3$ (*c* 0.8, $CHCl_3$); IR (Nujol): ν_{max} 1621, 1601, 1268, 1237, 742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.71 (t, 3H, $J=6.6$ Hz), 0.77–1.25 (m, 6H), 1.61 (d, 3H, $J=6.6$ Hz), 2.10–2.50 (m, 1H), 2.75–3.00 (m, 1H), 4.30 (q, 1H, $J=6.6$ Hz), 5.50 (s, 1H), 7.05–8.00 (m, 16H), 14.30 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8, 19.4, 22.1, 29.6, 30.4, 46.2, 57.8, 67.7, 116.5 120.9, 122.4, 126.4, 127.4, 127.7, 128.0, 128.2, 128.3, 128.5, 128.8, 129.0, 129.5, 129.6, 129.9, 131.9, 139.9, 156.2. Anal. calcd for $C_{30}H_{33}NO$ (423.6): C, 85.06; H, 7.85; N, 3.31. Found: C, 84.98; H, 7.94; N, 3.26%.

4.5.3. 1-[(1*R*)-Phenyl{benzyl[(1′*R*)-1′-phenylethyl]-amino}methyl]-2-naphthol, (*R*,*R*)-6c. White crystals; mp 153–156°C (hexane); $[\alpha]_D^{20}=-156.4$ (*c* 1.0, $CHCl_3$); IR (Nujol): ν_{max} 1621, 1601, 1454, 1268, 1236, 748 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.73 (d, 3H, $J=7.0$ Hz), 3.24 (d, 1H, $J=15.0$ Hz), 4.20 (d, 1H, $J=15.0$ Hz), 4.48 (q, 1H, $J=7.0$ Hz), 5.55 (s, 1H), 6.80–7.90 (m, 21H), 13.95 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.5, 50.7, 59.1, 68.3, 116.4, 119.8, 121.0, 122.5, 126.1, 126.6, 127.5, 127.6, 127.7, 128.0, 128.2, 128.5, 128.9, 129.0, 129.2, 129.4, 129.6, 130.0, 130.1, 131.8, 139.4, 155.9. Anal. calcd for $C_{32}H_{29}NO$ (443.6): C, 86.65; H, 6.59; N, 3.16. Found: C, 86.57; H, 6.66; N, 3.11%.

4.5.4. 1-[(1*R*)-Phenyl{ethyl[(1′*R*)-1′-phenylethyl]amino}methyl]-2-naphthol, (*R*,*R*)-6d. Oil; $[\alpha]_D^{20}=-146.0$ (*c* 1.1, $CHCl_3$, d.r. 76:24); IR (liquid film): ν_{max} 1621, 1601, 1583, 1268, 1237, 946 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.72 (t, 3H, $J=7.3$ Hz), 1.59 (d, 3H, $J=7.0$ Hz), 2.35–2.70 (m, 1H), 2.85–3.10 (m, 1H), 4.28 (q, 1H, $J=7.0$ Hz), 5.55 (s, 1H), 7.10–8.00 (m, 16H), 14.25 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 21.6, 40.8, 57.4, 67.4, 116.3, 120.0, 120.9, 122.4, 126.5, 127.6, 127.9, 128.2, 128.3, 128.6, 128.8, 128.9, 129.0, 129.5, 129.7, 131.9, 140.2, 156.2. Anal. calcd for $C_{27}H_{27}NO$ (381.5): C, 85.00; H, 7.13; N, 3.67. Found: C, 85.16; H, 7.01; N, 3.79%.

4.5.5. 1-[((1*R*)-Phenyl{but-3-enyl[(1′*R*)-1′-phenylethyl]-amino}methyl]-2-naphthol, (*R*,*R*)-6e. White crystals; mp 92–96°C (hexane); $[\alpha]_D^{20}=-290.6$ (*c* 1.1, $CHCl_3$); IR (Nujol): ν_{max} 1621, 1600, 1469. 1454, 1268, 1237, 743, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.52–1.89 (m, 2H), 1.62 (d, 3H, $J=7.0$ Hz), 2.25–2.55 (m, 1H), 2.88–3.15 (m, 1H), 4.31 (q, 1H, $J=7.0$ Hz), 4.76 (d, 1H, $J=17.2$ Hz), 4.91 (d, 1H, $J=9.9$ Hz), 5.38–5.65 (m, 1H), 5.48 (s, 1H), 7.10–7.90 (m, 16H), 13.80 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.0, 35.1, 46.0, 58.4, 67.9, 116.6, 120.1, 121.1, 122.6, 126.7, 128.0, 128.2, 128.3, 128.4, 128.7, 129.0, 129.2, 129.8, 130.2, 130.3, 132.0, 136.0, 139.7, 141.4, 156.5. Anal. calcd for $C_{29}H_{29}NO$ (407.5): C, 85.47; H, 7.17; N, 3.44. Found: C, 85.37; H, 7.03; N, 3.51%.

4.5.6. 1-[(1*R*)-Phenyl{allyl[(1′*R*)-1′-phenylethyl]amino}-methyl]-2-naphthol, (*R*,*R*)-6f. Oil; $[\alpha]_D^{20}=-234.3$ (*c* 1.0, $CHCl_3$); IR (liquid film): ν_{max} 1621, 1600, 1267, 1236, 781, 744 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.64 (d, 1H, $J=7.0$ Hz), 3.01–3.25 (m, 1H), 3.53 (dd, 1H, $J=15.4$, 5.9 Hz), 4.36 (q, 1H, $J=7.0$ Hz), 4.70 (dd, 1H, $J=17.2$, 1.3 Hz), 4.78 (dd, 1H, $J=10.3$, 1.3 Hz), 5.53–5.76 (m, 1H), 5.66 (s, 1H), 7.15–8.00 (m, 16H), 13.90 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3, 49.8, 58.0, 67.2, 116.7, 120.1, 121.1, 122.6, 126.6, 127.7, 127.9, 128.1, 128.2, 128.5, 128.6, 128.7, 128.9, 129.0, 129.2, 129.8, 132.0, 136.2, 140.0, 156.2. Anal. calcd for $C_{28}H_{27}NO$ (393.5): C, 85.46; H, 6.92; N, 3.56. Found: C, 85.37; H, 6.84; N, 3.69%.

4.6. General procedure for the enantioselective addition of diethylzinc to benzaldehyde promoted by enantiopure aminoalkylnaphthols 3a–i, 5j,k and 6a–f

Under a nitrogen atmosphere, a toluene solution of Et_2Zn (3.0 mmol, 1.1 M) was added to the appropriate aminonaphthol at 0°C and the solution was stirred at room temperature for 40 min. After cooling to 0°C, benzaldehyde (2.5 mmol) was added and the reaction mixture was stirred at room temperature for the time required. Aqueous hydrochloric acid (2 N) was added to quench the reaction at 0°C. The resulting mixture was extracted with CH_2Cl_2 and the organic layer was dried with anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude oil was purified by column chromatography on silica gel (cyclohexane/AcOEt). Enantiomeric excesses (% e.e.) were determined by GC analyses of the resulting alcohol on a chiral column MEGADEX DMP β (30% dimethylpentyl-β-cyclodextrine on OV1701, 25 m, 0.25 mm ID, 0.25 μm film). The configuration of the major enantiomer was assigned by comparison of the sign of the specific rotation of the alcohol with literature data.

Acknowledgements

Financial support from Ministero dell'Università e della Ricerca Scientifica e Tecnologica, Rome, and the University of Camerino (National Project 'Stereoselezione in Sintesi Organica. Metodologie ed applicazioni') is gratefully acknowledged.

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41. Enantiomeric purities (% e.e.) were determined by GC analyses of the resulting alcohols on capillary column MEGADEX DMP β (30% dimethylpentyl-β-cyclodextrin on OV 1701, 25 m, 0.25 mm ID, 0.25 μm film).